

I claim:

1. A method for generating a library of bi-ligands, comprising

(a) determining a common ligand to a conserved  
5 site in a receptor family;

(b) attaching an expansion linker to said common ligand, wherein said expansion linker has sufficient length and orientation to direct a second ligand to a specificity site of a receptor in said  
10 receptor family, to form a module; and

(c) generating a population of bi-ligands comprising a plurality of identical modules attached to variable second ligands.

2. The method of claim 1, further comprising:

(d) screening said population of bi-ligands  
15 for binding to a receptor in said receptor family; and

(e) identifying a bi-ligand that binds to and has specificity for said receptor.

3. The method of claim 1, wherein said  
20 population comprises three or more bi-ligands.

4. The method of claim 3, wherein said population comprises five or more bi-ligands.

5. The method of claim 1, wherein said receptor is an enzyme selected from the group consisting of kinases, dehydrogenases, oxidoreductases, GTPases, carboxyl transferases, acyl transferases, decarboxylases, transaminases, racemases, methyl transferases, formyl transferases, and  $\alpha$ -ketodecarboxylases.

6. The method of claim 1, wherein said receptor family binds a cofactor selected from the group consisting of nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide phosphate, thiamine pyrophosphate, flavin adenine dinucleotide, flavin mononucleotide, pyridoxal phosphate, coenzyme A, tetrahydrofolate adenosine triphosphate, guanosine triphosphate and S-adenosyl methionine.

7. The method of claim 1, wherein said expansion linker has approximate C2 symmetry.

8. The method of claim 7, wherein said expansion linker has perfect C2 symmetry.

9. A method for identifying a population of bi-ligands to receptors in a receptor family, comprising

(a) determining a common ligand to a conserved site in the receptor family;

(b) attaching an expansion linker to said common ligand, wherein said expansion linker has sufficient length and orientation to direct a second ligand to a specificity site of a receptor in said receptor family, to form a module; and

(c) generating a population of bi-ligands, wherein said bi-ligand comprises said module and a second ligand linked by said expansion linker.

10. The method of claim 9, further comprising:

5 (d) screening said population of bi-ligands for binding to a receptor in said receptor family;

(e) identifying a bi-ligand that binds to and has specificity for said receptor; and

10 (f) repeating steps (d) and (e) to identify a bi-ligand that binds to and has specificity for a second receptor in said receptor family.

11. The method of claim 9, wherein said receptor is an enzyme selected from the group consisting of kinases, dehydrogenases, oxidoreductases, GTPases, carboxyl transferases, acyl transferases, decarboxylases, transaminases, racemases, methyl transferases, formyl transferases, and  $\alpha$ -ketodecarboxylases.

12. The method of claim 9, wherein said receptor family binds a cofactor selected from the group consisting of nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide phosphate, thiamine pyrophosphate, flavin adenine dinucleotide, flavin mononucleotide, pyridoxal phosphate, coenzyme A, tetrahydrofolate adenosine triphosphate, guanosine triphosphate and S-adenosyl methionine.

13. The method of claim 9, wherein said expansion linker has approximate C2 symmetry.

14. The method of claim 13, wherein said expansion linker has perfect C2 symmetry.

15. A method for identifying a bi-target ligand to a receptor, comprising

5 (a) identifying a first bi-ligand to a first receptor in a receptor family, wherein said bi-ligand comprises a common ligand to a conserved site in a receptor family and a first specificity ligand to said first receptor;

10 (b) identifying a second bi-ligand to a second receptor in said receptor family, wherein said bi-ligand comprises said common ligand and a second specificity ligand to said second receptor; and

15 (c) generating a bi-target ligand comprising said common ligand, said first specificity ligand and said second specificity ligand, whereby said bi-target ligand can bind to said first receptor and said second receptor.

20 16. The method of claim 15, wherein said receptor is an enzyme selected from the group consisting of kinases, dehydrogenases, oxidoreductases, GTPases, carboxyl transferases, acyl transferases, decarboxylases, transaminases, racemases, methyl transferases, formyl transferases, and  $\alpha$ -ketodecarboxylases.

17. The method of claim 15, wherein said receptor family binds a cofactor selected from the group consisting of nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide phosphate, thiamine pyrophosphate, flavin adenine dinucleotide, flavin mononucleotide, pyridoxal phosphate, coenzyme A, tetrahydrofolate adenosine triphosphate, guanosine triphosphate and S-adenosyl methionine.

18. The method of claim 15, wherein said expansion linker has approximate C2 symmetry.

19. The method of claim 18, wherein said expansion linker has perfect C2 symmetry.

20. A library of bi-ligands comprising a common ligand to a conserved site in a receptor family and an expansion linker attached to said common ligand, wherein said expansion linker has sufficient length and orientation to direct a second ligand to a specificity site of a receptor in said receptor family to form a module; and a specificity ligand attached to said expansion linker.

21. The library of claim 20, wherein said population comprises three or more bi-ligands.

22. The library of claim 20, wherein said population comprises five or more bi-ligands.

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23. The library of claim 20, wherein said receptor is an enzyme selected from the group consisting of kinases, dehydrogenases, oxidoreductases, GTPases, carboxyl transferases, acyl transferases, decarboxylases, transaminases, racemases, methyl transferases, formyl transferases, and  $\alpha$ -ketodecarboxylases.

24. The library of claim 20, wherein said receptor family binds a cofactor selected from the group consisting of nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide phosphate, thiamine pyrophosphate, flavin adenine dinucleotide, flavin mononucleotide, pyridoxal phosphate, coenzyme A, tetrahydrofolate adenosine triphosphate, guanosine triphosphate and S-adenosyl methionine.

25. The library of claim 23, wherein said expansion linker has approximate C2 symmetry.

26. The library of claim 25, wherein said expansion linker has perfect C2 symmetry.

27. A population of two or more bi-ligands, comprising:

(a) at least one bi-ligand to a first receptor comprising a common ligand to a conserved site in a receptor family and a specificity ligand to a specificity site of said first receptor in said receptor family; and

(b) at least one bi-ligand to a second receptor comprising said common ligand and a specificity ligand to a specificity site of said second receptor in said receptor family,

wherein said common ligand and said specificity ligand are linked by an expansion linker of sufficient length and orientation to direct said specificity ligand to a specificity site of said receptor.

5           28. The population of two or more bi-ligands of claim 27, wherein said receptor is an enzyme selected from the group consisting of kinases, dehydrogenases, oxidoreductases, GTPases, carboxyl transferases, acyl transferases, decarboxylases, transaminases, racemases,  
10 methyl transferases, formyl transferases, and  $\alpha$ -ketodecarboxylases.

          29. The population of two or more bi-ligands of claim 27, wherein said receptor family binds a cofactor selected from the group consisting of  
15 nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide phosphate, thiamine pyrophosphate, flavin adenine dinucleotide, flavin mononucleotide, pyridoxal phosphate, coenzyme A, tetrahydrofolate adenosine triphosphate, guanosine triphosphate and S-adenosyl  
20 methionine.

          30. The population of two or more bi-ligands of claim 27, wherein said expansion linker has approximate C2 symmetry.

          31. The population of two or more bi-ligands  
25 of claim 30, wherein said expansion linker has perfect C2 symmetry.

          32. A bi-target ligand, comprising:

(a) a common ligand to a conserved site in a receptor family;

(b) a first specificity ligand to a specificity site of a first receptor in said receptor family; and

(c) a second specificity ligand to a specificity site of a second receptor in said receptor family,

wherein said common ligand and said specificity ligands are linked by an expansion linker of sufficient length and in an orientation directing said first specificity ligand to said specificity site of said first receptor and said second specificity ligand to said specificity site of said second receptor.

33. The bi-target ligand of claim 32, wherein said receptor is an enzyme selected from the group consisting of kinases, dehydrogenases, oxidoreductases, GTPases, carboxyl transferases, acyl transferases, decarboxylases, transaminases, racemases, methyl transferases, formyl transferases, and  $\alpha$ -ketodecarboxylases.

34. The bi-target ligand of claim 32, wherein said receptor family binds a cofactor selected from the group consisting of nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide phosphate, thiamine pyrophosphate, flavin adenine dinucleotide, flavin mononucleotide, pyridoxal phosphate, coenzyme A, tetrahydrofolate adenosine triphosphate, guanosine triphosphate and S-adenosyl methionine.

35. The bi-target ligand of claim 32, wherein said expansion linker has approximate C2 symmetry.



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| NUMBER | DATE | DESCRIPTION | AMOUNT | BALANCE |
|--------|------|-------------|--------|---------|
| 1      | 1890 | Jan 1       | 100.00 | 100.00  |
| 2      | 1890 | Feb 1       | 50.00  | 50.00   |
| 3      | 1890 | Mar 1       | 25.00  | 25.00   |
| 4      | 1890 | Apr 1       | 12.50  | 12.50   |
| 5      | 1890 | May 1       | 6.25   | 6.25    |
| 6      | 1890 | Jun 1       | 3.12   | 3.12    |
| 7      | 1890 | Jul 1       | 1.56   | 1.56    |
| 8      | 1890 | Aug 1       | .78    | .78     |
| 9      | 1890 | Sep 1       | .39    | .39     |
| 10     | 1890 | Oct 1       | .19    | .19     |
| 11     | 1890 | Nov 1       | .09    | .09     |
| 12     | 1890 | Dec 1       | .05    | .05     |
| 13     | 1891 | Jan 1       | .02    | .02     |
| 14     | 1891 | Feb 1       | .01    | .01     |
| 15     | 1891 | Mar 1       | .01    | .01     |
| 16     | 1891 | Apr 1       | .01    | .01     |
| 17     | 1891 | May 1       | .01    | .01     |
| 18     | 1891 | Jun 1       | .01    | .01     |
| 19     | 1891 | Jul 1       | .01    | .01     |
| 20     | 1891 | Aug 1       | .01    | .01     |
| 21     | 1891 | Sep 1       | .01    | .01     |
| 22     | 1891 | Oct 1       | .01    | .01     |
| 23     | 1891 | Nov 1       | .01    | .01     |
| 24     | 1891 | Dec 1       | .01    | .01     |
| 25     | 1892 | Jan 1       | .01    | .01     |
| 26     | 1892 | Feb 1       | .01    | .01     |
| 27     | 1892 | Mar 1       | .01    | .01     |
| 28     | 1892 | Apr 1       | .01    | .01     |
| 29     | 1892 | May 1       | .01    | .01     |
| 30     | 1892 | Jun 1       | .01    | .01     |
| 31     | 1892 | Jul 1       | .01    | .01     |
| 32     | 1892 | Aug 1       | .01    | .01     |
| 33     | 1892 | Sep 1       | .01    | .01     |
| 34     | 1892 | Oct 1       | .01    | .01     |
| 35     | 1892 | Nov 1       | .01    | .01     |
| 36     | 1892 | Dec 1       | .01    | .01     |
| 37     | 1893 | Jan 1       | .01    | .01     |
| 38     | 1893 | Feb 1       | .01    | .01     |
| 39     | 1893 | Mar 1       | .01    | .01     |
| 40     | 1893 | Apr 1       | .01    | .01     |
| 41     | 1893 | May 1       | .01    | .01     |
| 42     | 1893 | Jun 1       | .01    | .01     |
| 43     | 1893 | Jul 1       | .01    | .01     |
| 44     | 1893 | Aug 1       | .01    | .01     |
| 45     | 1893 | Sep 1       | .01    | .01     |
| 46     | 1893 | Oct 1       | .01    | .01     |
| 47     | 1893 | Nov 1       | .01    | .01     |
| 48     | 1893 | Dec 1       | .01    | .01     |
| 49     | 1894 | Jan 1       | .01    | .01     |
| 50     | 1894 | Feb 1       | .01    | .01     |
| 51     | 1894 | Mar 1       | .01    | .01     |
| 52     | 1894 | Apr 1       | .01    | .01     |
| 53     | 1894 | May 1       | .01    | .01     |
| 54     | 1894 | Jun 1       | .01    | .01     |
| 55     | 1894 | Jul 1       | .01    | .01     |
| 56     | 1894 | Aug 1       | .01    | .01     |
| 57     | 1894 | Sep 1       | .01    | .01     |
| 58     | 1894 | Oct 1       | .01    | .01     |
| 59     | 1894 | Nov 1       | .01    | .01     |
| 60     | 1894 | Dec 1       | .01    | .01     |
| 61     | 1895 | Jan 1       | .01    | .01     |
| 62     | 1895 | Feb 1       | .01    | .01     |
| 63     | 1895 | Mar 1       | .01    | .01     |
| 64     | 1895 | Apr 1       | .01    | .01     |
| 65     | 1895 | May 1       | .01    | .01     |
| 66     | 1895 | Jun 1       | .01    | .01     |
| 67     | 1895 | Jul 1       | .01    | .01     |
| 68     | 1895 | Aug 1       | .01    | .01     |
| 69     | 1895 | Sep 1       | .01    | .01     |
| 70     | 1895 | Oct 1       | .01    | .01     |
| 71     | 1895 | Nov 1       | .01    | .01     |
| 72     | 1895 | Dec 1       | .01    | .01     |
| 73     | 1896 | Jan 1       | .01    | .01     |
| 74     | 1896 | Feb 1       | .01    | .01     |
| 75     | 1896 | Mar 1       | .01    | .01     |
| 76     | 1896 | Apr 1       | .01    | .01     |
| 77     | 1896 | May 1       | .01    | .01     |
| 78     | 1896 | Jun 1       | .01    | .01     |
| 79     | 1896 | Jul 1       | .01    | .01     |
| 80     | 1896 | Aug 1       | .01    | .01     |
| 81     |      |             |        |         |